PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61F 13/02 — A1

(11) International Publication Number: **WO 97/40792**

(43) International Publication Date: 6 November 1997 (06.11.97)

(21) International Application Number: PCT/US97/07104

(22) International Filing Date: 29 April 1997 (29.04.97)

(30) Priority Data:
08/640,371 30 April 1996 (30.04.96) US

(71) Applicant *(for all designated States except US)*: THERATECH, INC. [US/US]; 417 Wakara Way, Salt Lake City, UT 84108 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SRINIVASAN, Venkateshwaran [IN/US]; 2411 Emerson Avenue, Salt Lake City, UT 84108 (US). EBERT, Charles, D. [US/US]; 1515 S. Cantebury Drive, Salt Lake City, UT 84108 (US).

(74) Agents: CIOTTI, Thomas, E. et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: TRANSDERMAL ADMINISTRATION OF STEROID HORMONES USING DIETHANOLAMIDES OF C_{12}-C_{18} FATTY ACIDS AS PERMEATION ENHANCERS

(57) Abstract

Matrix-type transdermal patches for administering steroids comprising a matrix of one or more steroid hormones, a pressure sensitive adhesive and a diethanolamide of a C_{12}-C_{18} fatty acid as a permeation enhancer. These diethanolamides provide unexpectedly superior permeation enhancement as compared to related known enhancers in such patches.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TRANSDERMAL ADMINISTRATION OF STEROID HORMONES USING DIETHANOLAMIDES OF C_{12}-C_{18} FATTY ACIDS AS PERMEATION ENHANCERS

TECHNICAL FIELD

The present invention is in the field of transdermal/transmucosal drug delivery. More particularly it concerns the use of dialkanolamides of fatty acids to enhance the transdermal administration of steroid hormones from a pressure sensitive adhesive matrix.

BACKGROUND ART

Steroid hormones such as progestins, estrogens, and androgens have poor skin permeability. Therefore, in order to administer steroids transdermally or transmucosally at therapeutically effective rates through a reasonably sized area of skin or mucosa, it is necessary to use permeation enhancers in combination with the steroid.

A number of patents describe using permeation enhancers to increase the permeability of skin to steroid hormones. U.S. Patent Nos. 5,164,190 and 5,152,997 describe the use of a combination of subsaturation concentration and permeation enhancers to increase the flux of steroid drugs across skin. The exemplified enhancers include glycerol dioleate, glycerol monooleate, methyl laurate, oleic acid, and ethanol.

U.S. Patent Nos. 4,906,169 and 5,023,084 describe laminated composites for coadministering an estrogen and progestin transdermally. The estrogen is contained in a polymer layer and the progestin is contained in an underlying adhesive layer. Polyacrylic, polyisobutylene and silicone adhesives are mentioned. These patents also teach that a permeation enhancer can be included in the adhesive. "Saturated and unsaturated fatty acids and their esters, alcohols, monoglycerides, acetate, diethanolamides and N,N-dimethylamides . . ." are mentioned as enhancers. N-Decyl alcohol and capric acid are taught as preferred enhancers.

U.S. Pat. Nos. 4,818,540 and 5,296,230 also describe laminated composites for administering estrogens or progestins transdermally. In these composites the steroid is contained in a polymer layer. An adhesive layer underlies the polymer layer for affixing the composite to the skin. The patent teaches that the adhesive layer may contain permeation enhancers. The same enhancers that are taught in the '169 and '084 patents discussed above are also described in these patents.

U.S. Patent No. 5,314,694 discloses transdermal delivery devices but not a matrix type as disclosed herein where the drug and permeation enhancer is dissolved or dispersed in an adhesive which also serves to also affix the patch to the skin. The devices disclosed in U.S. Patent No. 5,314,694 are typical reservoir type patches containing the drug and/or enhancer in a reservoir and a separate adhesive layer affixes the reservoir is referred to the skin. The disclosure does not teach that a diethanolamide of a C_{12}-C_{18} fatty acid is uniquely effective in enhancing the permeability of steroid hormones in a pressure sensitive adhesive matrix.

PCT Publication WO 94/21262 describes the use of diethanolamides of fatty acids as permeation enhancers in combination with alprazolam. The diethanolamide and alprazolam are formulated in a nonadhesive polymeric reservoir.

U.S. Patent No. 5,252,334 teaches away from the use of permeation enhancers for the transdermal delivery of steroids.

Even though various enhancers have been used previously to increase the rate at which steroids permeate through skin, there is still a need to find enhancers that permit even higher rates to be achieved. Better enhancers may allow the steroids, particularly testosterone, to be formulated in simple single matrix patches of relatively small size. This will enable less expensive patches that are more cosmetically acceptable.

DISCLOSURE OF THE INVENTION

The present invention is based on applicants' discovery that diethanolamides of C_{12}-C_{18} fatty acids are unexpectedly superior to other permeation enhancers with respect to enhancing the permeability of steroid hormones that are administered transdermally from a pressure sensitive adhesive matrix.

Accordingly, one aspect of the invention is a method of enhancing the transdermal administration of a steroid hormone from a pressure sensitive adhesive matrix comprising coadministering a diethanolamide of a C_{12}-C_{18} fatty acid from said matrix.

Another aspect of this invention is the use of a highly pure composition of lauramide DEA for enhancing the transdermal administration of a steroid hormone from a pressure sensitive adhesive matrix.

Another aspect of the invention is a matrix for administering a steroid hormone transdermally comprising a mixture of: a) a pressure sensitive adhesive; b) a steroid hormone; and c) a diethanolamide of a C_{12}-C_{18} fatty acid.

Yet another aspect of the invention is a transdermal patch for administering a steroid hormone comprising a laminated composite of:

a) a backing layer; and

b) a matrix layer adapted to be placed in diffusional contact with skin or mucosa comprising a mixture of:

(i) a pressure sensitive adhesive;

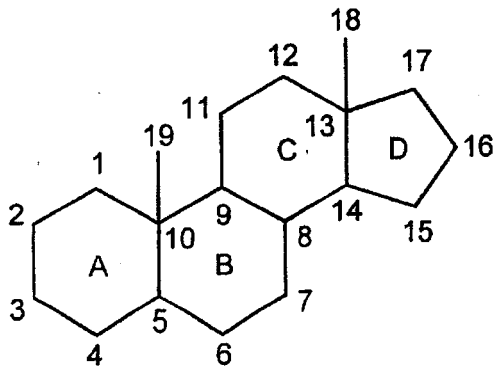
(ii) a steroid hormone; and

(iii) a diethanolamide of a C_{12}-C_{18} fatty acid.

MODES FOR CARRYING OUT THE INVENTION

As used herein the term "transdermal" intends percutaneous and transmucosal (e.g. transbuccal) administration, i.e., passage of steroid through unbroken skin or mucosa into circulation.

Structurally "steroids" are the class of compounds all related through the cyclic nuclei they contain, i.e., a partly or completely hydrogenated 17 H-cyclopentanophenanthrene nucleus, the general formula for which is given below:



Steroid hormones can be natural, synthetic or semi-synthetic and can be classified according to their biological function as:

Progestagens, examples of which are (without limitation) progesterone, norethindrone acetate, norgestrel, levo-norgestrel, norethindrone, desogestrel, and gestodene.

Glucocorticoids, examples of which are (without limitation) corticol, corticone, hydrocortisone, betamethasone, dexamethasone, prednisone, predisolone and triamcinolone.

Mineralocorticoids, examples of which are (without limitation) aldosterone and desoxycorticosterone.

Estrogens, examples of which are (without limitation) 17β estradiol and ethynyl estradiol.

Androgens, examples of which are (without limitation) testosterone, methyl testosterone, dihydrotestosterone and androsteinedione.

Cardiac glycosides, examples of which are (without limitation) digoxin and digitoxin.

Depending upon the condition being treated, a combination of steroid hormones may be administered. For instance, in providing hormone replacement therapy to females combination of an estrogen and a progestagen or an estrogen and an androgen (e.g., estradiol and testosterone) may be used.

A "therapeutically effective amount" of steroid intends an amount that provides the desired pharmacological result. These amounts are known by those skilled in the art. For instance, in the case of administering testosterone to males, the therapeutically effective amount will typically be about 1 to 10 mg/day.

As used herein the terms "permeation enhancement" and "enhancement" are used interchangeably and describe an increase in the permeability of skin or mucosa to a steroid hormone. Permeation enhancement results in an increase in the flux of steroid through skin or mucosa. Skin flux may be measured in vitro using the procedure described in the examples, *infra*. A "skin/mucosa permeation enhancing amount" of diethanolamide of a C_{12}-C_{18} fatty acid is intended to mean an amount that results in steroid flux increase of at

least about 15%, more usually 30% to 300% relative to steroid flux in the absence of an enhancer.

As used herein the term "diffusional contact" means that the matrix is either directly or indirectly in contact with the skin or mucosa in a manner in which there is a diffusional pathway by which the steroid(s) can migrate from the matrix to the skin or mucosa.

The adhesive component of this invention are referred to as "matrix patches" containing for example a hydrocarbon solvent-compatible polyacrylate or a hydrocarbon solvent compatible adhesive. The adhesive reservoir or matrix can be a pressure-sensitive adhesive such as polyisobutylene, silicone, polyacrylate or other pressure sensitive adhesive acceptable for use as a matrix for a transdermal patch. The adhesive component of the matrix is preferably a hydrocarbon solvent-compatible polyacrylate, particularly a copolymer of 2-ethylhexyl acrylate and one or more other monomers such as vinyl acetate, acrylic acid, N-vinyl-2-pyrrolidone, 2-hydroxyethyl acrylate, butylacrylate, octylacrylate, styrene, methyl methacrylate, methacrylic acid, maleic acid, acrylamide and N-methylol acrylamide. Embodiments of such adhesives are available commercially from a number of sources, e.g. GELVA® adhesives from Monsanto Chemical Co., MORSTIK® adhesives from Morton Thiokol, Inc., Duro-Tak® adhesives from National Starch, and TSR adhesive from Sekisui.

The diethanolamides that are employed as permeation enhancers in the invention are diethanolamides of C_{12}-C_{18} fatty acids.

The fatty acid may be saturated or unsaturated and preferably has an even number of carbon atoms. Examples that are useful in the invention are the diethanolamides of lauric, tridecylic, myristic, pentadecylic, palmitic, stearic, palmitoleic, oleic and linoleic acids. A mixture of such diethanolamides may be used. Lauramide diethanol ("lauramide DEA") is preferred. The diethanolamide component of the matrix will typically constitute 0.5% to 50% of the matrix, preferably 2.5% to 15%. Percentage of the components of the matrix are expressed on a dry weight basis. It has been found that commercially available lauramide DEA have verying degrees of purity. Substantially pure compositions of lauramide DEA are preferred. As used herein, "substantially pure" is defined as having a greater than about 75% lauramide DEA in the composition wherein "%" refers to area percent as determined by HPLC according to Example 9, infra.. More preferred is a

composition containing greater than about 85% lauramide DEA and most preferred is greater than about 90% lauramide DEA.

The steroid will normally constitute 0.1% to 30%, preferably 0.5% to 10% of the matrix.

The matrix may be formulated by mixing the adhesive (which is typically obtained in solution), steroid(s), and diethanolamide in the appropriate proportions, casting the solution onto a substrate (e.g., a backing or release liner layer) and drying the cast layer of solution to drive off the solvent. The backing layer will typically comprise an occlusive polymer layer, combination of polymer layers, or combination of polymeric and metallic layers. Backing materials are well known in the transdermal patch art.

In addition to the matrix and backing, the transdermal patches of this invention will also include a release liner layer. Release liner materials are also well known in the transdermal patch art.

The invention is further illustrated by the following examples. These examples are not intended to limit the invention in any manner.

EXAMPLES

Adhesive Matrix Preparation

Pressure sensitive polyacrylate adhesive matrix systems containing steroids and in some cases additional components were prepared from acrylate copolymer solutions in organic solvents as follows. First, the solid content of the adhesive solution was determined by placing a known weight of solution in a weighed aluminum dish and evaporating the solvents overnight in a 70°C convection oven. The solid adhesive content of the solution was calculated by dividing the adhesive solid weight after drying by the total solution weight. Second, a weighed quantity of adhesive solution was added to a glass bottle and the solid adhesive weight was calculated from the known solid fraction of the given adhesive solution. Steroid compounds and enhancers were weighed and mixed with the adhesive solution in the quantities necessary to achieve the desired dry matrix composition. The solution containing the adhesive copolymer and other components was mixed (usually overnight). Next, approximately 8 ml of the solution was dispensed on a silanized polyester release liner and cast with a 10 mil (0.25 mm) gap casting knife. The

cast was dried in a 70°C convection oven for 15 minutes to yield a dried film of approximately 2 mil (0.05 mm) thickness, then 3 mil (0.08 mm) thick polyethylene film was laminated onto the dried adhesive cast. These matrix systems were then used to conduct *in vitro* skin flux experiments as described below.

Skin Flux Studies

In vitro skin flux studies were conducted using human cadaver epidermal membrane in modified Franz non-jacketed diffusion cells. The epidermal membrane (stratum corneum and epidermis) had been separated from the human cadaver whole skin (epidermal membrane and dermis) by the heat-separation method of Kligman and Christopher (*Arch. Dematol.* 88:702 (1963)). This method involves the exposure of the full-thickness skin to water at 60 °C for a time period of 60 seconds. After this period, the epidermal membrane was gently peeled off the dermis and stored for later use in aluminum foil at -5 °C. Prior to skin permeation experiments, the silanized release liner was removed from the adhesive matrix system and the adhesive was affixed to the stratum corneum side of the thawed epidermal membrane which was then cut to an appropriate size and placed between the two halves of the diffusion cell with the stratum corneum facing the donor compartment. The receiver compartment was filled with an appropriate receiver medium to maintain sink conditions for the drug (e.g. 0.02% (w/v) sodium azide and 0.5% (w/v) Tween 40 for testosterone), and the diffusion cell was placed in a temperature controlled circulating water bath calibrated to maintain the surface temperature of the skin at 32 °C. The receiver compartment was constantly stirred by a magnetic stir-bar in the receiver compartment agitated by a magnetic stirring module placed under the water bath. At predetermined sampling intervals (usually 6, 12, and 24 hours), the entire contents of the receiver compartment were collected for drug quantitation and the receiver compartment was filled with fresh receiver solution, taking care to eliminate any air bubbles at the skin/solution interface.

The cumulative amount of drug permeated per unit area at any time t (Q_t, $\mu g/cm^2$) was determined from the following equation:

$$Q_t = \sum_{t=0}^{t} \frac{C_t V}{A},$$

where C_t ($\mu g/cm^3$) is the concentration of the receiver compartment at sample time t (h), V is the volume of the receiver compartment of the diffusion cell (6.3 cm^3), and A is the diffusional area of the cell (0.64 cm^2).

Example 1

Testosterone is a naturally occurring steroid hormone which is administered transdermally for treatment of primary or secondary hypogonadism in males. Pressure sensitive adhesive matrix systems containing testosterone and lauramide diethanol (DEA) as an enhancer were compared to systems using lauric acid, lauryl alcohol, glycolic acid, and esters of lauric acid. All matrix systems were prepared in a medical-grade acrylic adhesive (Duro-Tak 87-2516) according to the methods described above and contained 3% by weight testosterone and 10% by weight enhancer. The results of skin flux experiments using these matrix systems are summarized in Tables 1-3.

Table 1

Daily *In Vitro* Permeation of Testosterone, Mean ± SD, [$\mu g/(cm^2*24h)$]

All Systems are Duro-Tak 2516/Testosterone/Enhancer 87/3/10% (w/w)

		Enhancer			
Skin Characteristics*	Number of Diffusion Cells	Lauramide DEA	Lauric Acid	Lauryl Alcohol	Methyl Laurate
46 yr, Male RPL	4	52.1 ± 4.9	41.9 ± 2.1	40.8 ± 7.3	29.0 ± 2.8
66 yr, Male RPL	4	63.5 ± 14.0	39.1 ± 5.9	43.4 ± 5.8	27.0 ± 5.6
38 yr, Female LPL	4	49.1 ± 8.7	35.6 ± 5.8	39.0 ± 7.5	28.4 ± 6.7
65 yr, Male LPL	4	57.2 ± 6.1	57.6 ± 2.7	45.1 ± 5.9	46.7 ± 2.8
57 yr, Male LPL	4	68.8 ± 11.8	50.2 ± 5.5	80.2 ± 11.5	47.7 ± 5.3
63 yr, Male RPL	4	59.9 ± 2.4	37.4 ± 6.0	43.2 ± 11.9	26.8 ± 4.0
All Skins	24	58.4 ± 7.3	43.6 ± 8.6	48.6 ± 15.6	34.3 ± 10.1

* Age, Sex, Site (RPL=Right Posterior Leg, LPL=Left Posterior Leg)

Table 2

Daily *In Vitro* Permeation of Testosterone, Mean ± SD, [μg/(cm^2*24h)]

All Systems are Duro-Tak 2516/Testosterone/Enhancer 87/3/10% (w/w)

Skin Characteristics	Number of Diffusion Cells	Enhancer Lauramide DEA	Enhancer Glycerol Monolaurate
46 yr, Male RPL	4	52.1 ± 4.9	37.6 ± 5.5
57 yr, Male LPL	4	68.8 ± 11.8	63.6 ± 4.1
63 yr, Male RPL	4	59.9 ± 2.4	46.7 ± 8.0
All Skins	12	60.3 ± 8.4	49.3 ± 13.2

* Age, Sex, Site (RPL=Right Posterior Leg, LPL=Left Posterior Leg)

Table 3

Daily *In Vitro* Permeation of Testosterone, Mean ± SD, [μg/(cm^2*24h)]

Skin Characteristics*	Number of Diffusion Cells	Composition: Duro-Tak 2516/Testosterone/Enhancer % (w/w) No Enhancer 97/3/0	Lauramide DEA 87/3/10	Glycolic Acid 87/3/10	Sorbitan Monooleate** 87/3/10
63 yr, Male, RAL	4	28.3 ± 4.1	40.6 ± 4.3	35.0 ± 7.2	37.2 ± 3.9
65 yr, Male, RAL	4	35.2 ± 5.4	47.4 ± 2.7	26.1 ± 0.8	22.3 ± 3.3
38 yr, Female, LPL	4	15.5 ± 1.3	48.9 ± 6.5	23.4 ± 4.3	23.2 ± 1.0
All Skins	12	26.3 ± 10.0	45.7 ± 4.4	28.2 ± 6.1	27.6 ± 8.4

* Age, Sex, Site (RAL=Right Anterior Leg, LPL=Left Posterior Leg)

** Sorbitan monooleate=oleic acid ester of sorbitol (Arlacel® 80)

Table 4

Daily *In Vitro* Permeation of Testosterone, Mean ± SD, [μg/(cm^2*24h)]

All Systems are Duro-Tak 2516/Testosterone/Enhancer 92/3/5% (w/w)

Skin Characteristics*	Number of Diffusion Cells	Enhancer Lauramide DEA	Lauryl PCA**
47 yr, Male, RPL	4	59.4 ± 9.0	44.0 ± 8.0
24 yr, Female, LPL	4	55.3 ± 5.6	38.5 ± 5.0
47 yr, Male, LPL	4	81.6 ± 4.7	48.6 ± 8.6
All skins	12	65.4 ± 14.2	43.7 ± 5.1

* Age, Sex, Site (RPL=Right Posterior Leg, LPL=Left Posterior Leg)

** Lauryl PCA=Lauryl alcohol, pyrrolidinone carboxylic acid ester (Laurydone®)

The data in Tables 1-4 show that a system using the diethanolamide derivative of lauric acid increases testosterone flux about 20% more than lauryl alcohol and lauric acid monoglyceride, 35% more than lauric acid, 50% more than the pyrrolidinone carboxylic acid ester (PCA) of lauryl alcohol, and about 70% more than the methyl ester of lauric acid, the sorbitan ester of oleic acid, and glycolic acid. These results indicate that fatty acid diethanolamide is unexpectedly superior at enhancing transdermal permeation of testosterone in a matrix system relative to α-hydroxy acids, fatty acids, fatty alcohols, fatty acid alkyl esters, fatty alcohol PCA esters, fatty acid monoglycerides, and fatty acid sorbitol esters--all of which are known in the art as transdermal permeation enhancers.

Example 2

Testosterone flux from matrix systems and hydroalcoholic gel systems was evaluated using Lauramide DEA and the methyl ester of lauric acid as enhancers. Hydroalcoholic solutions of 50 mg/ml testosterone in 50% by volume alcohol, USP (190 proof ethanol), 15% water, 30% glycerin, and 5% enhancer were prepared and mixed until the drug was fully dissolved. The solution was then gelled with 3% (w/w) carbomer (Pemulen TR-2) which was neutralized with 0.2 N sodium hydroxide to a pH of 4 to 5. The resulting gels were clear and visually homogeneous.

Skin flux experiments for the hydroalcoholic gels were similar to those conducted with the adhesive matrix systems with the following exceptions. Prior to skin permeation experiments, the epidermal membrane was cut to an appropriate size and placed between the two halves of the diffusion cell with the stratum corneum facing the donor compartment. The receiver compartment was filled with 0.02% (w/v) sodium azide in water, and the diffusion cell was placed in a circulating water bath calibrated to maintain the temperature of the skin surface at 32°C, and allowed to hydrate overnight. After hydration, the sodium azide solution in the receiver compartment was removed and replaced with an appropriate solution to maintain sink conditions for testosterone through the duration of the experiment (0.02% (w/v) sodium azide and 0.5% (w/v) Tween 40 in water). A sample of the hydroalcoholic gel (75 µl) was then pipetted into a cavity created by placing a polyethylene washer over the stratum corneum surface. This cavity was covered with an occlusive polyethylene which was then clamped in place. Sampling of the

receiver solution at predetermined intervals was carried out as described above for the adhesive matrix skin flux experiments. Results from the *in vitro* skin flux experiments carried out with these gels are summarized in Table 5.

Adhesive matrices containing 3% by weight testosterone and 10% by weight enhancer were prepared in Duro-Tak 87-2516 as described previously. Skin flux experiments using the matrix systems on the same skin sources as those shown in Table 5 were conducted and the results from these experiments are shown in Table 6.

Table 5

Daily *In Vitro* Permeation of Testosterone, Mean ± SD, [μg/(cm^2*24h)]

All Systems are Alcohol/Water/Glycerin/Enhancer 50/15/30/5% (v/v)

Skin Characteristics*	Number of Diffusion Cells	Enhancer Lauramide DEA	Methyl Laurate
60 yr, Male, LPL	4	72.5 ± 19.1	224.8 ± 41.0
45 yr, Male, LPL	4	158.2 ± 52.0	424.1 ± 82.8
63 yr, Male, LPL	4	215.9 ± 40.0	313.6 ± 53.6
All Skins	12	148.9 ± 72.2	320.8 ± 99.9

* Age, Sex, Site (LPL=Left Posterior Leg)

Table 6

Daily *In Vitro* Permeation of Testosterone. Mean ± SD, [μg/(cm^2*24h)]

All Systems are Duro-Tak 2516/Testosterone/Enhancer 92/3/5% (w/w)

Skin Characteristics*	Number of Diffusion Cells	Enhancer Lauramide DEA	Methyl Laurate
60 yr, Male, LPL	4	46.3 ± 6.8	24.1 ± 6.2
45 yr, Male, LPL	4	89.1 ± 16.5	48.4 ± 11.8
63 yr, Male, LPL	4	95.5 ± 8.3	52.7 ± 10.2
All Skins	12	76.9 ± 26.8	41.7 ± 15.4

* Age, Sex, Site (LPL=Left Posterior Leg)

The data in Table 5 show that in a hydroalcoholic gel lauramide DEA does not exhibit unusual flux enhancement relative to the methyl ester of lauric acid. The results in Table 6 confirm that the unusual flux enhancement for testosterone exhibited by lauramide

DEA relative to other known permeation enhancers occurs specifically in pressure sensitive adhesive matrix systems.

Example 3

Norethindrone acetate (NEA) is a female progestin steroid hormone. Adhesive matrix systems containing NEA and NEA with Lauramide DEA (Cyclomide® LE), sorbitan monolaurate (Arlacel® 20), or sorbitan monooleate (Arlacel® 80) as an enhancer were prepared as described above. The matrix systems consisted of 10% by weight NEA and 0 or 15% of the enhancer in Duro-Tak 80-1194 or Duro-Tak 80-1054. The results of *in vitro* skin flux experiments on these matrix systems are summarized in Table 7 and Table 8.

Table 7

Daily *In Vitro* Permeation of NEA, Mean ± SD, [μg/(cm^2*24h)]

		Composition: Duro-Tak 80-1194/NEA/Enhancer			
Skin Characteristics*	Number of Diffusion Cells	No Enhancer 90/10 % (w/w)	Lauramide DEA 75/10/15% (w/w)	Sorbitan Monolaurate 75/10/15% (w/w)	Sorbitan Monooleate 75/10/15% (w/w)
67 yr, Male	4	5.4 ± 0.5	15.9 ± 1.7	13.2 ± 0.8	7.3 ± 0.4
76 yr, Male	4	4.7 ± 0.5	16.8 ± 0.6	9.1 ± 1.4	8.4 ± 4.2
All Skins	8	4.5 ± 0.7	15.5 ± 0.7	11.1 ± 2.8	7.5 ± 0.7

* Age, Sex

Table 8

Daily *In Vitro* Permeation of NEA, Mean ± SD, [μg/(cm^2*24h)]

		Composition: Duro-Tak 80-1054/NEA/Enhancer			
Skin Characteristics*	Number of Diffusion Cells	No Enhancer 90/10 % (w/w)	Lauramide DEA 75/10/15% (w/w)	Sorbitan Monolaurate 75/10/15% (w/w)	Sorbitan Monooleate 75/10/15% (w/w)
67 yr, Male	4	6.6 ± 1.5	18.3 ± 2.9	12.3 ± 1.2	9.8 ± 2.5

* Age, Sex

The data in Tables 7 and 8 indicate that use of lauramide DEA as an enhancer increases the flux of NEA from an adhesive matrix system about 3-fold relative to an adhesive matrix with NEA alone. In addition, use of lauramide DEA as an enhancer increases the flux of NEA from 40 to 50% more on average than matrix systems containing sorbitan monolaurate and about 2-fold more than matrix systems containing sorbitan monooleate. These results show that lauramide DEA is an unexpectedly superior permeation enhancer for NEA in a matrix system, showing significantly more flux enhancement than the two sorbitol esters tested--both of which are know permeation enhancers.

Example 4

Estradiol is a naturally occurring female steroid hormone which is administered transdermally for female hormone replacement therapy. Adhesive matrix systems containing estradiol and estradiol with lauramide DEA (Cyclomide® LE), sorbitan monolaurate (Arlacel® 20), or sorbitan monooleate (Arlacel® 80) as an enhancer were prepared as described above. The matrix systems consisted of 4% by weight estradiol and 0 to 15% of the enhancer in a medical grade acrylic copolymer adhesive (Duro-Tak 80-1194 or 80-1070). The results of *in vitro* skin flux experiments on these matrix systems are summarized in Tables 9-11.

Table 9

Daily *In Vitro* Permeation of Estradiol, Mean ± SD, [μg/(cm^2*24h)]

		Composition: Duro-Tak 80-1194/Estradiol/Enhancer			
Skin Characteristics*	Number of Diffusion Cells	No Enhancer 96/4 % (w/w)	Lauramide DEA 81/4/15% (w/w)	Sorbitan Monolaurate 81/4/15% (w/w)	Sorbitan Monooleate 81/4/15% (w/w)
47 yr, Male	4	18.1	92.9	49.0	81.2
76 yr, Male	4	2.4	25.0	10.0	12.0
All Skins	8	10.3 ± 11.1	59.0 ± 48.0	29.5 ± 27.6	46.6 ± 48.9

* Age, Sex

Table 10

Daily *In Vitro* Permeation of Estradiol, Mean ± SD, [μg/(cm^2*24h)]

		Composition: Duro-Tak 80-1194/Estradiol/Enhancer			
Skin Characteristics*	Number of Diffusion Cells	No Enhancer 96/4 % (w/w)	Lauramide DEA 81/4/15% (w/w)	Sorbitan Monolaurate 81/4/15% (w/w)	Sorbitan Monooleate 81/4/15% (w/w)
47 yr, Male	4	25.6	90.9	49.5	52.6
76 yr, Male	4	6.9	26.6	6.6	20.1
All Skins	8	16.3 ± 13.2	58.8 ± 45.5	28.1 ± 30.3	36.4 ± 23.0

* Age, Sex

Table 11

Daily *In Vitro* Permeation of Estradiol, Mean ± SD, [μg/(cm^2*24h)]

		Composition: Duro-Tak 80-1070/Estradiol/Enhancer			
Skin Characteristics*	Number of Diffusion Cells	No Enhancer 96/4 % (w/w)	Lauramide DEA 81/4/15% (w/w)	Sorbitan Monolaurate 81/4/15% (w/w)	Sorbitan Monooleate 81/4/15% (w/w)
47 yr, Male	4	18.6	70	48.7	34.1
76 yr, Male	4	5.8	19.6	5.3	8.4
All Skins	8	12.2 ± 9.1	44.8 ± 35.6	27.0 ± 30.7	21.3 ± 18.2

* Age, Sex

The results in Tables 9-11 demonstrate that lauramide DEA increases the flux about 4 to 5-fold relative to estradiol alone in an adhesive matrix system. The cumulative drug delivered from the system with lauramide DEA is typically 1.5 to 2 times greater than from systems using the know permeation enhancers, sorbitan monolaurate and sorbitan monooleate.

Example 5

The effect of fatty acid diethanolamides differing in the fatty acid group were evaluated in matrix systems containing various steroids. The fatty acid diethanolamides used as enhancers were lauramide DEA (Cyclomide® DEA), stearamide DEA (Cyclomide® DS 280), or cocamide DEA (Alkamide® KD). Cocamide DEA is derived from coconut oil and contains palmitamide DEA. The systems consisted of 4% by weight estradiol or 3% by weight testosterone and 0 to 15% of the enhancer in Duro-Tak 87-2516 or Duro-Tak 80-1194. The results of *in vitro* skin flux experiments on these matrix systems are summarized in Tables 12 and 13.

Table 12

Daily *In Vitro* Permeation of Testosterone, Mean ± SD, [μg/(cm^2*24h)]

Skin Characteristics*	Number of Diffusion Cells	Composition: Duro-Tak 87-2516/Testosterone/Enhancer No Enhancer 97/3 % (w/w)	Lauramide DEA 92/3/5 % (w/w)	Cocamide DEA** 92/3/5 % (w/w)
47 yr, Male, RPL	4	25.4 ± 4.2	57.1 ± 18.8	43.1 ± 7.9
47 yr, Male, LPL	4	38.2 ± 5.9	63.2 ± 4.9	61.9 ± 4.5
53 yr, Male, RPL	4	37.7 ± 6.1	60.3 ± 1.9	61.3 ± 4.6
	12	33.7 ± 7.3	60.2 ± 3.1	55.4 ± 10.7

* Age, Sex, Site (RPL=Right Posterior Leg, LPL=Left Posterior Leg)
** Cocamide DEA=Coconut Fatty Acid, Diethanolamide

Table 13

Daily *In Vitro* Permeation of Estradiol, Mean ± SD, [μg/(cm^2*24h)]

Number of Diffusion Cells	Composition: Duro-Tak 80-1194/Estradiol/Enhancer No Enhancer 96/4/0 % (w/w)	Lauramide DEA 81/4/15 % (w/w)	Stearamide DEA** 81/4/15 % (w/w)
4	6.2 ± 0.7	9.4 ± 2.1	9.8 ± 6.5

** Stearamide DEA=Stearic Acid, Diethanolamide

The results above indicate that changes in the fatty acid component of the diethanolamides (within the C_{12} to C_{18} range) do not significantly change the flux enhancement observed in estradiol or testosterone skin flux.

Example 6

Transdermal flux enhancement of steroids using fatty acid diethanolamide was compared to flux enhancement using triethanolamine. Adhesive matrices containing 3% by weight testosterone as a model steroid and 5% by weight lauramide DEA or triethanolamine were prepared in Duro-Tak 87-2516, and the results of *in vitro* skin flux experiments using these matrices are shown in Table 14.

Table 14

Daily *In Vitro* Permeation of Testosterone, Mean ± SD, [μg/(cm^2*24h)]

All Systems are Duro-Tak 2516/Testosterone/Enhancer 92/3/5% (w/w)

Skin Characteristics*	Number of Diffusion Cells	Enhancer Lauramide DEA	Triethanolamine
42 yr, Male RPL	4	75.4 ± 7.9	33.2 ± 2.4
53 yr, Male LPL	4	40.4 ± 6.9	13.7 ± 1.6
All Skins	8	57.9 ± 24.7	23.5 ± 13.8

* Age, Sex, Site (RPL=Right Posterior Leg, LPL=Left Posterior Leg)

The data in Table 14 provide evidence that the fatty acid component of alkanoic acid diethanolamides is required for transdermal flux enhancement of steroid molecules from pressure sensitive adhesives.

Example 7

Transdermal flux enhancement of testosterone and estradiol from a matrix system was evaluated using fatty acid amides with differing amine components. Adhesive matrices containing 3% by weight testosterone or 1.5% by weight estradiol were prepared in an acrylic copolymer adhesive (Duro-Tak 87-2516, or 80-1070). The fatty acid amides tested were lauramide DEA (Alkamide® LE), cocamide MEA (Alkamide® CME), lauramide MEA (Alkamide® L-203), lauramide MIA (Alkamide® LIPA/C), lauric acid N,N-dimethylamide, and lauric acid N,N-diethylamide. Results from *in vitro* flux experiments on these matrix systems are summarized in Tables 15-17.

Table 15

Daily *In Vitro* Permeation of Testosterone, Mean ± SD, [μg/(cm^2*24h)]

All Systems are Duro-Tak 2516/Testosterone/Enhancer 92/3/5% (w/w)

Skin Characteristics*	Number of Diffusion Cells	Enhancer Lauramide DEA	Cocamide MEA**	Lauramide MEA**	Lauramide MIA**
42 yr, Male, RPL	4	75.4 ± 7.9	50.6 ± 1.7	52.0 ± 11.6	50.2 ± 10.0
53 yr, Male, LPL	4	40.4 ± 6.9	22.2 ± 3.9	18.2 ± 5.2	25.5 ± 6.0
All Skins	8	57.9 ± 24.7	36.4 ± 20.1	35.1 ± 23.9	37.9 ± 17.5

* Age, Sex, Site (RPL=Right Posterior Leg, LPL=Left Posterior Leg)

** Cocamide MEA=Coconut Fatty Acid, Monoethanolamide; Lauramide MEA=Lauric Acid, Monoethanolamide; Lauramide MIA=Lauric Acid, Monoisopropylamide

Table 16

Daily *In Vitro* Permeation of Estradiol, Mean ± SD, [μg/(cm^2*24h)]

All Systems are Duro-Tak 1070/Estradiol/Enhancer 93.5/1.5/5% (w/w)

Skin Characteristics*	Number of Diffusion Cells	Enhancer Lauramide DEA	Lauric Acid N,N-Dimethylamide
69 yr, Female, NA	4	15.6 ± 1.0	7.8 ± 0.5
64 yr, Female, NA	4	4.8 ± 0.9	5.1 ± 1.7
43 yr, Female, NA	4	15.3 ± 1.4	8.4 ± 0.7
69 yr, Female, NA	4	14.9 ± 3.2	5.5 ± 1.6
61 yr, Male, LAL	4	13.2 ± 1.6	9.4 ± 1.9
55 yr, Female, LPL	4	3.9 ± 0.1	2.3 ± 0.3
All Skins	24	11.3 ± 5.4	6.4 ± 2.6

* Age, Sex, Site (LAL=Left Anterior Leg, LPL=Left Posterior Leg, NA=Site information not available)

Table 17

Daily *In Vitro* Permeation of Estradiol, Mean ± SD, [μg/(cm^2*24h)]

All Systems are Duro-Tak 1070/Estradiol/Enhancer 93.5/1.5/5% (w/w)

Skin Characteristics*	Number of Diffusion Cells	Enhancer Lauramide DEA	Lauric Acid N,N-Diethylamide
69 yr, Female, NA	4	14.9 ± 3.2	5.5 ± 1.6
61 yr, Male, LAL	4	13.2 ± 1.6	9.4 ± 1.9
55 yr, Female, LPL	4	3.9 ± 0.1	2.3 ± 0.3
All Skins	24	11.3 ± 5.4	4.8 ± 2.5

* Age, Sex, Site (LAL=Left Anterior Leg, LPL=Left Posterior Leg, NA=Site information not available)

The results in Tables 15-17 show that fatty acid diethanolamides are significantly superior to the other fatty acid amides tested at increasing the transdermal flux of testosterone and estradiol. Monoethanolamides, monoisopropanolamides, and dimethylamides and diethylamides do not exhibit the same degree of flux enhancement for steroid compounds.

Example 8

Transdermal flux enhancement of non-steroidal compounds, oxybutynin and diclofenac, from a matrix system was evaluated using Lauramide DEA and several other known permeation enhancers. Adhesive matrices containing oxybutinin or diclofenac were prepared in an acrylic copolymer adhesive (Seksui TSR). The matrices contained 10% (w/w) of one of the following enhancers lauramide DEA (Alkamide® LE), glycerol monolaurate , lauric acid methyl ester, or lauryl alcohol. Results from *in vitro* flux experiments on these matrix systems are summarized in Tables 18 and 19.

Table 18

Daily *In Vitro* Permeation of Oxybutynin, Mean ± SD, [μg/(cm^2*24h)]

All Systems are TSR/Oxybutynin/Enhancer 70/20/10% (w/w)

Skin Characteristics*	Number of Diffusion Cells	Enhancer Lauramide DEA	Glycerol Monolaurate	Methyl Laurate	Lauryl Alcohol
60 yr, Male, RAL	4	22.8 ± 7.8	56.8 ± 11.9	39.9 ± 5.9	40.5 ± 4.3
68 yr, Male, LPL	4	19.8 ± 6.9	30.2 ± 2.6	22.5 ± 3.3	45.0 ± 9.0
57 yr, Male, LPL	4	21.2 ± 4.3	47.8 ± 6.7	27.1 ± 3.8	30.1 ± 1.4
All Skins	12	21.3 ± 1.5	44.9 ± 13.5	29.8 ± 9.0	38.5 ± 7.7

* Age, Sex, Site (RPL=Right Posterior Leg, RAL=Right Anterior Leg)

Table 19

Daily *In Vitro* Permeation of Diclofenac, Mean ± SD, [μg/(cm^2*24h)]

All Systems are TSR/Diclofenac/Enhancer 97/10/3% (w/w)

Skin Characteristics*	Number of Diffusion Cells	Enhancer Lauramide DEA	Glycerol Monolaurate	Methyl Laurate	Lauryl Alcohol
64 yr, Male, RPL	4	9.1 ± 0.8	10.0 ± 1.2	14.2 ± 1.2	8.4 ± 1.1
55 yr, Male, RPL	4	8.5 ± 1.3	11.0 ± 3.2	28.4 ±11.2	17.8 ± 3.3
47 yr, Male, LAL	4	24.6 ± 1.7	22.0 ± 4.3	21.3 ± 3.6	31.0 ± 3.4
All Skins	12	14.1 ± 9.1	14.3 ± 6.7	21.3 ± 7.1	19.1 ± 1.3

* Age, Sex, Site (RPL=Right Posterior Leg, LAL=Left Anterior Leg)

Oxybutynin permeation from the system containing Lauramide DEA is lower than the permeation from systems containing glycerol monolaurate, methyl laurate, or lauryl alcohol as enhancers. These results suggest that the unusual transdermal flux enhancement of alkanoic acid diethanolamides is specific to steroidal compounds.

Diclofenac permeation from the system containing lauramide DEA is similar to or lower than the permeation from systems containing glycerol monolaurate methyl laurate, or lauryl alcohol as enhancers. These results are further evidence that the unusual

transdermal flux enhancement of alkanoic acid diethanolamides is specific to steroidal compounds.

Example 9

Applicants have discovered that compositions containing highly pure formulations of lauramide DEA unexpectedly enhances the transdermal flux of drugs, including steroids. Table 20 lists the commercially available lauramide DEA formulations that were evaluated for purity.

Table 20

Material	Lot Number	Supplier
Alkamide LE	CH5G962	Rhone-Poulenc
Aminon L-02	1904	Kao Chemical
Prophan AA-62EX	X503271	Sanyo Kasei Co.

Table 21 shows the results of HPLC analysis of the above noted commercially available lauramide DEA formulations. A (3.0 x 150) mm column C-18 Symmetry (available from Waters Corporation, Milford MA, USA) with Symmetry guard was run at ambient temperature flow rate of 1.2 ml/minute, detection λ at 210 nm. The mobile phase of the column was a 40:60 (v:v) water:acetonitrile solution.

Table 21

HPLC Area Fractions Showing Purity of Lauramide DEA Materials.

Manufacturer	Lauramide DEA	Impurity #1	Impurity #2	Impurity #3	Impurity #4	Impurity #5
Rhone-Poulenc Alkamide LE	59.5±0.6%	0.9±0.4%	17.2±0.4%	2.5±0.02%	7.8±0.1%	11.6±0.1%
Kao Aminon L-02	86.8±0.1%	4.9±0.1%	7.8±0.03%			
Sanyo Kasei Prophan	98.2±0.1%	0.6±0.03%	0.3±0.1%	0.7±0.03%		

Transdermal flux enhancement of testosterone from a matrix system was evaluated using lauramide DEA of low purity (Alkamide LE (Rhone-Poulenc)) and high purity

(Prophan (Sanyo Kasei)). Adhesive matrices containing 6% by weight testosterone and 7.5% lauramide DEA were prepared in an acrylic copolymer adhesive 86.5% (TSR Adhesive). Table 22 reports the results of invitro skin flux experiments on these matrices.

Table 22

In Vitro Permeation Enhancement of Testosterone in a Matrix System Using High-Purity Lauramide DEA.

Skin Source	Alkamide LE $\mu g/cm^2*day$	Prophan $\mu g/cm^2*day$	Enhancement Factor Prophan/Alk LE
CIN 2406-01-8	44.12	53.11	1.20
JM102596-9	49.21	51.09	1.04
LM111296-8	31.47	40.99	1.30
BM033096-2	72.16	79.63	1.10
CIN 2382-01-5	59.83	68.97	1.15
CIN 2960-10-04	68.03	52.03	0.76
CIN 2363-01-4	35.5	42.76	1.20
CIN 2472-01-7	47.02	34.05	0.72
CIN 2502-01-14	51.05	67.97	1.33
D-424-03	68.03	73.35	1.08
HH080396-9	73.44	91.17	1.24
JQ071396-17	57.27	75.2	1.31
CIN 2576-01-23	34.6	49.45	1.43
CN 2617-10-09	25.78	28.66	1.11
D-424-11	67.05	93.33	1.39
Mean (All Skins)	52.30	60.12	1.16
SD	15.75	20.07	0.20
95% Conf. Int.			1.05-1.27

This difference in means is significant ($p<0.05$, 2-Way ANOVA).

Testosterone permeation from the systems containing greater than 85% pure lauramide DEA is, in most instances, greater than permeation from systems containing less pure (i.e., less than 75%) lauramide DEA.

Modifications of the above-described modes for carrying out the invention that are obvious to those of skill in the field of transdermal drug delivery are intended to be within the scope of the following claims.

CLAIMS

We claim:

1. A matrix type transdermal patch for administering a steroid hormone transdermally comprising:

a) a backing layer; and

b) a matrix layer adapted to be placed in diffusional contact with skin or mucosa comprising a mixture of

(i) a pressure sensitive adhesive;

(ii) a therapeutically effective amount of a steroid hormone; and

(iii) a skin permeation enhancing amount of a diethanolamide of a C_{12}-C_{18} fatty acid.

2. The patch of claim 1 wherein the steroid hormone is a progestagen, estrogen, androgen, or combination thereof and the matrix is a hydrocarbon-compatible polyacrylate polymer.

3. The patch of claim 2 wherein the steroid hormone is testosterone, the polyacrylate is a copolymer of 2-ethylhexylacrylate and at least one other monomer, and the fatty acid is lauric acid.

4. The patch of claim 1, wherein the skin permeation enhancer is lauramide DEA.

5. The patch of claim 4 wherein the lauramide DEA is substantially pure.

6. A pressure sensitive adhesive matrix for use in administering a steroid hormone transdermally comprising a mixture of:

a) a pressure sensitive adhesive;

b) a therapeutically effective amount of a steroid hormone; and

c) a permeation enhancing amount of a diethanolamide of a C_{12}-C_{18} fatty acid.

7. The matrix of claim 6 wherein the steroid hormone is a progestagen, estrogen, androgen, or combination thereof, and the pressure sensitive adhesive matrix is a hydrocarbon compatible polyacrylate.

8. The matrix of claim 7 wherein the steroid hormone is testosterone, the polyacrylate is a copolymer of 2-ethylhexylacrylate and at least one other monomer, and the fatty acid is lauric acid.

9. A method of enhancing the transdermal administration of a steroid hormone from a pressure sensitive adhesive matrix comprising coadministering a permeation enhancing amount of a diethanolamide of a C_{12}-C_{18} fatty acid from said matrix.

10. The method of claim 9 wherein the steroid hormone is a progestagen, estrogen, androgen, or combination thereof, and the pressure sensitive adhesive matrix is a hydrocarbon compatible polyacrylate.

11. The method of claim 10 wherein the steroid hormone is testosterone, the polyacrylate is a copolymer of 2-ethylhexylacrylate and at least one other monomer, and the fatty acid is lauric acid.

INTERNATIONAL SEARCH REPORT

I...national application No.
PCT/US97/07104

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61F 13/02
US CL : 424/448
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/448, 447, 449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,314,694 A (GALE et al) 24 May 1994, column 8, lines 6-65 and column 7, 141-50.	1, 4-6, and 9
Y	US 4,906,475 A (KIM) 06 March 1990, column 5, line 38 through column 6, line 44.	1-9
Y	US 5,252,334 A (CHIANG et al) 12 October 1993, column 3, line 1 through column 4, line 37.	1-9

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
30 MAY 1997	0 8 JUL 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer GABRIELLE PHELAN Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07104

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,362,497 A (YAMADA et al) 08 November 1994, column 7, line 35 and column 12, line 5 through column 14, line 5.	1-9
Y	US 5,460,820 A (EBERT et al) 24 October 1995, column 1, line 1 through column 6, line 65.	1-9
Y, P	US 5,554,381 A (ROOS et al) 10 September 1996, column 1, line 52 through column 2, line 48.	1-9
Y, P	US 5,560,922 A (CHIEN et al) 01 October 1996, column 5, line 62 through column 7, line 30 and column 14, line 32 through column 16, line 32.	1-9